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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/674,237	EGAN ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the c ver sheet with the c rrespondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 March 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-58* is/are pending in the application.

4a) Of the above claim(s) *11-18,20-49 and 54-58* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,19 and 50-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *01/14/02* .
4) ☒ Interview Summary (PTO-413) Paper No(s). *03/19/03* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's election of group I, claims 1-10, 19, 50-53, species human Ese1, in paper of 09/30/03 with traverse in paper of 09/30/03 is acknowledged and entered.

Claims 1-58 are pending in the instant application and Claims 11-18, 20-49, 54-58 have been withdrawn from further consideration by the Examiner under 37 CFR 1.142(b) as being drawn to non-elected invention.

Group I, Claims 1-10, 19, 50-53, SEQ ID NO:1, 2, and a nucleic acid encoding the amino acid sequence of SEQ ID NO:3, both species human and murine Ese1, are currently under prosecution, since species murine Ese1 has been rejoined with species human Ese1, because there is no art found for human Ese1.

The traverse is on the ground that it would not be a burden to examine the claims concurrently and that the species requirement is unreasonably burdensome for Applicant, as it requires Applicant to file at least 92 separate applications.

It is noted that the restriction requirement of 92 groups is not due to species requirement. The 92 groups are patentably distinct for reasons set forth in previous Office action, require separate searches, and it would be a serious burden for the Examiner to search all the groups together.

Further, species human Ese1 has been rejoined with species murine Ese1, because no art is found for human Ese1. Therefore, arguments concerning species requirement by Applicant are moot.

The restriction requirement is still deemed to be proper, and therefore made Final.

Accordingly, Claims 1-10, 19, 50-53, SEQ ID NO:1, 2, and a nucleic acid encoding the amino acid sequence of SEQ ID NO:3, species human and murine Ese1, are examined in the instant application, wherein Claims 1-10, 19, 50-53 are examined only to the extent of SEQ ID NOs: 1 and 2, and a nucleic acid encoding the polypeptide of SEQ ID NO:3. It is noted that the splice variants were not elected.

SEQUENCE RULE COMPLIANCE

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. 1.821-25 for the following reasons:

Tables 1-2 on pages 79-82 and figure 2B recite sequences without sequence identification numbers.

Appropriate amendment is required.

OBJECTION

1. Claims 1-3 are objected to, because part of claims 1-3 are drawn to non-elected invention, i.e. the splice variants, which belong to group 2.

2. Claims 6-7 are objected to, because part of claims 6-7 are drawn to non-elected sequences, i.e. SEQ ID NOs: 22 and 23, which belong to group 2.

REJECTION UNDER 35 USC 101, UTILITY

35 U.S.C. 101 reads as follows:

"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Claims 1-10, 19, 50-53 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial asserted utility or a well established utility.

Claims 1-10, 19, 50-53 are drawn to:

1) An isolated nucleic acid comprising a nucleotide sequence encoding a mammalian, murine or human Ese1, which is a genomic sequence, a cDNA sequence, a polydeoxyribonucleic acid sequence, or a polyribonucleic acid sequence. Said nucleic acid encoding a protein of SEQ ID NO:3 or comprises the sequence of SEQ ID NO:1 or 2 (claims 1-6).

2) An isolated nucleic acid comprising a nucleotide sequence of at least 10 consecutive nucleotides, selected from the group consisting of SEQ ID NO:1, 2, and a complementary sequence thereof, wherein said sequence is used as a probe or a primer (claims 7-8).

3) A recombinant vector comprising said nucleic acid of claim 1, 7, and a host cell comprising said vector (claims 9-10, 50-51), and

4) A process for recombinantly producing murine Ese1 protein (claims 19, 52-53).

The specification discloses the murine Ese1 nucleotide sequence of SEQ ID NO:1 and its coding sequence of SEQ ID NO:2, encoding the polypeptide of SEQ ID NO:3. The specification also discloses a splice variant of the murine Ese1 of SEQ ID NO:22 and its coding sequence of SEQ ID NO:23, encoding the variant protein of SEQ ID NO:24. The specification further discloses that overexpression of the murine Ese1 of SEQ ID NO:1 or 2 blocks endocytosis in Cos-1 cell in culture, and that overexpression of Dynamin II may override the Ese1 induced endocytic block (p.22, first paragraph). The specification further discloses that using two hybrid system and co-immunoprecipitation, the encoded murine Ese1of SEQ ID NO:3 binds to proteins such as Eps15, a protein necessary for endocytosis, the cbl-b oncoprotein, Dynamin II, Jerky, hnRNP-K, SAP49 and SOS-1 (p.18-20). The specification suggests the murine Ese1 functions in a complex with Eps15 protein to regulate endocytosis together (p.20, lines 3-4). The specification suggests that the murine Ese1 is also involved in intracellular signaling processes, based on the identification of potential phosphorylation sites on the murine Ese1 of SEQ ID NO:1, wherein said processes are likely to lead to altered cellular activity (p.20, lines 6-9).

The specification suggests that since the murine Ese1of SEQ ID NO:1 is involved in endocytosis, involving protein-protein interaction and intracellular signaling, Ese1 protein is most likely involved in a myriad of clinical conditions and processes which are very likely to include but not be limited to 1) regulation of endocytosis, 2) cell division

and cancer since Esp15 and cbl to which Ese1 binds to are oncoproteins, 3) cell migration, since regulation of the actin cytoskeleton is required for many forms of cell migration, 4) cell polarity, plane of cell division, and cell fate, since Esp15 binds to Numb in vivo, which is required for these processes, 5) RNA localization, since several RNA binding proteins have been identified in the present screen, and 6) viral infection and life cycle, since Eps15 binds to RAB, a cellular cofactor for HIV Rev (p.23, second paragraph).

The specification contemplates therapies against viral infection and virally-induced disease states, since Ese1 may play an important role in viral infection. The specification discloses that HIV-NEF binds to SH3 domains, wherein NEF induces coated pit formation, it is possible that Ese1, having SH3 domain, may bind to NEF and are involved in NEF function. The specification contemplates inhibition of Ese1-NEF interactions, and thus inhibiting endocytosis and viral infection and virally induced disease state (p.23, third paragraph).

The specification contemplates treating various nervous disorder due to abnormal or altered synaptic transmission, because Ese1 regulates endocytosis, and binds to Jerky, a protein required to prevent epilepsy in mice (p.23, last paragraph, bridging p.24).

The specification contemplates that altering the rate of endocytosis by targeting Ese1 protein, the cell proliferative effect of growth factor receptor stimulation, leading to cell proliferation and possibly cancer, could be counteracted (p.24, second paragraph).

The specification suggests that abnormal pattern of cell division and migration may involve altered Ese1 function and altered endocytosis, since abnormal cell division and cell migration as seen in several diseases involves cell cytoskeleton, and endocytosis is known to involve in rearrangement of the intracellular skeleton.

The specification suggests that developmental diseases can occur as a result of abnormal remodeling of cytoskeleton, leading to altered intracellular signaling.

The specification discloses that the protein encoded by Ese1 has utility for the preparation of antibodies, indentification of binding partners of Ese1, and for diagnostic and therapeutic methods (p.4, lines 17-20).

The specification contemplates gene therapy, and immunotherapy, for treating disorders involving abnormal endocytosis, vesicular trafficking and abnormal regulation of the actin cytoskeleton, which may include disorders such as those involving abnormal cell division, cancer, abnormal cell migration, viral infection, abnormal tissue development, and abnormal synaptic disorders (p.26, last paragraph, bridging p.27).

The specification contemplates using antisense based strategies for therapeutic drug design (p.27, paragraph before last)

The specification contemplates screening for diseases involving abnormal Ese1, such as cancer, abnormal cell division, abnormal cell migration, viral infection, abnormal receptor signaling, abnormal tissue development and abnormal synaptic transmission disorders (p.28, last paragraph to p.32).

The specification however does not disclose that human or murine Ese1 is actually overexpressed or underexpressed in any of the diseases which are claimed to

be due to abnormal endocytosis, such as abnormal pattern of cell division and migration. There is no actual data showing a correlation between human or murine Ese1 and any disease, such a difference between the level of Ese1 mRNA in a disease such as abnormal cell division, cancer, abnormal cell migration, viral infection, abnormal tissue development, and abnormal synaptic disorders as compared to corresponding normal control cell , such that one could use the claimed human or murine Ese1 as a diagnosis marker for the above diseases.

Further, there is no actual data of successful treating of any disease in any model, such as treating abnormal cell division, cancer, abnormal cell migration, viral infection, abnormal tissue development, and abnormal synaptic disorders, such that one could use the claimed human or murine Ese1 for treating the above diseases.

The instant application lacks specific and substantial utility for the following reasons: Although overexpression of the murine Ese1 of SEQ ID NO:1 blocks endocytosis in Cos-1 cell in culture, no practical use of the claimed sequences has been shown in the specification.

It is noted that the asserted utilities for human Ese1 or the murine Ese1 of SEQ ID NO:1 or 2, such as production of and screening of agonists, antibodies and antagonists apply to many unrelated polypeptide structures sequences. Therefore the asserted utilities are not considered "specific" utilities, i.e. they are not specific to human Ese1 or the murine Ese1 of SEQ ID NOs: 1 or 2.

Further, concerning the intended use of human Ese1 or murine Ese1 of SEQ ID NO:1 or 2 or the encoded polypeptide thereof for diagnosis and treating cancer, without

any objective evidence that human Ese1 or the murine Ese1 of SEQ ID NO:1 or 2 is differentially expressed in cancer tissues versus normal cells, or that human Ese1 or the murine Ese1 of SEQ ID NO:1 or 2 could be used for treating cancer, one cannot assess the claimed invention, because of the following reasons:

a) One cannot determine that human Ese1 or the murine Ese1 of SEQ ID NO:1 or 2 would be differentially expressed in cancer tissues versus normal cells, and further experimentation is required to show that human Ese1 or the murine Ese1 of SEQ ID NO:1 or 2 could be useful in diagnosis of cancer, since a change in the level of expression of a gene in a tumor as compared to normal corresponding cells is unpredictable. It is well known in the art that not every gene in a cancer cell is affected in carcinogenesis, such as mutation or changes in expression as compared to normal control cells. For example, Stanton, P et al, 1994, Br J Cancer, 70: 427-433 teach that the level of expression of epidermal growth factor receptor (EGFR) cannot be predicted from cell lines or tumors (p.432, second column, last paragraph), and that from ten tumors from which the cell lines are derived, only two of the tumors display elevated levels of EGFR, BICR6 and BICR18 proteins (table V on page 430, and first column, last paragraph of page 430) In other words, not only the level EGFR, BICR6 and BICR18 proteins are the same as normal control in 8 tumors, the rest of other proteins in table V are not different from normal control in all ten tumors. Similarly, Iehle, C et al, 1999, J Steroid Biochem Mol Biol, 68: 189-195, teach that although the level of 5-alpha-reductase-1 is increased in prostate cancer tissue, the level of the isoform5-alpha-reductase-2 is the same as that of normal prostate (abstract). Abbaszadegan, M R, et

al, 1994, Cancer Res, 54: 4676-4679, teach that the level of multidrug resistance-associated protein (MRP) detected in malignant hematopoietic cells is similar to the level found in normal hematopoietic cells (p.4678, second column, last 6 lines of second paragraph).

Thus further experimentation is required to show that human Ese1 or the murine Ese1 of SEQ ID NO:1 or 2 could be useful in diagnosis of cancer, since change in level of expression of a gene in a tumor as compared to normal corresponding cells is unpredictable, and one cannot determine that human Ese1 or the murine Ese1 of SEQ ID NO:1 or 2 would be differentially expressed in cancer tissues versus normal cells,

2) One cannot determine that human Ese1 or the murine Ese1 of SEQ ID NO:1 or 2 would be effective in treating cancer, and further experimentation is required to show that human Ese1 or the murine Ese1 of SEQ ID NO:1 or 2 could be useful in treating cance, since cancer therapy is unpredictable. Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). Further, the refractory nature of cancer to drugs is well known in the art. Jain (Sci. Am., 1994, 271:58-65) teaches that tumors resist penetration by drugs (p.58, col 1) and that scientists need to put expanded effort into uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of

common solid tumors (p. 65, col 3). Curti (Crit. Rev. in Oncology/Hematology, 1993, 14:29-39) teaches that solid tumors resist destruction by chemotherapy agents and that although strategies to overcome defense mechanisms of neoplastic cells have been developed and tested in a number of patients, success has been limited and further teaches that it is certainly possible that cancer cells possess many as yet undefined additional molecular mechanisms to defeat chemotherapy treatment strategies and if this is true, designing effective chemotherapeutic regimens for solid tumors may prove a daunting task (para bridging pages 29-30) and concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (p. 36, col 2). In addition, Hartwell et al (Science, 1997, 278:1064-1068) teach that an effective chemotherapeutic must selectively kill tumor cells, that most anticancer drugs have been discovered by serendipity and that the molecular alterations that provide selective tumor cell killing are unknown and that even understanding the detailed molecular mechanism by which a drug acts often provides little insight into why the treated tumor cell dies (para bridging pages 1064-1065) and Jain (cited supra) specifically teaches that systemic treatment typically consists of chemotherapeutic drugs that are toxic to dividing cells (p. 58, col 2, para 2).

Thus since cancer therapy is unpredicatable, one cannot determine that human Ese1 or the murine Ese1 of SEQ ID NO:1 or 2 would be effective in treating cancer, and further experimentation is required to show that human Ese1 or the murine Ese1 of SEQ ID NO:1 or 2 could be useful in treating cancer .

Because of the above, the claimed human Ese1 or the murine Ese1 of SEQ ID NO:1 or 2 lack specific and substantial utility.

Further although the specification suggests that murine Ese1 of SEQ ID NO:1 could bind to various proteins, such as Esp15, which regulates endocytosis and the actin cytoskeleton, or Jerky, which is required to prevent epilepsy in mice, or Esp15 and cbl which are oncoproteins, or Numb which is involved in cell polarity, plane of cell division, and cell fate, there is no data teaching as to what effect that binding would have. Binding to a protein per se does not mean that the murine Ese1 of SEQ ID NO:1 would have the same function as the protein to which Ese1 binds.

Neither the specification nor any art of record teaches a utility for human or the murine Ese1 of SEQ ID NO: 1 or 2. They do not teach a relationship to any specific diseases or establish any involvement in the etiology of any specific diseases. Thus, further experimentation is required to show that human or murine Ese1 is actually associated with these diseases, and could be used for diagnosis or treating these diseases.

For reasons set forth above the disclosure satisfies none of the criteria for a specific and substantial utility *See In re Kirk*, 153 USPO 48, 53 (CCPA 1967) (quoting the Board of Patent Appeals, 'We do not believe that it was the intention of the statutes to require the Patent Office, the courts, or the public to play the sort of guessing game that might be involved if an applicant could satisfy the requirements of the statutes by indicating the usefulness of a claimed compound in terms of possible use so general as to be meaningless and then, after his research or that of his competitors has definitely

ascertained an actual use for the compound, adducing evidence intended to show that a particular specific use would have been obvious to men skilled in the particular art to which this use relates.'). In *Brenner*, the Court approved a rejection for failure to disclose any utility for a compound where the compound was undergoing screening for possible tumor-inhibiting effects and an adjacent homologue of the compound had proven effective. *Brenner*, 148 USPO at 690. Here, there is no evidence that the claimed human Ese1 or the murine Ese1 of SEQ ID NOs:1 or 2 has any utility.

The specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the disclosed nucleic acids. Because the claimed invention is not supported by a specific, substantial asserted utility for the reasons set forth, credibility of any utility cannot be assessed.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT

The following is a quotation of the first paragraph of 35 U.S.C. 112:

"The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

Claims 1-10, 19, 50-53 are rejected under 35 U.S.C. 112, first paragraph.

Specifically, since the claimed invention is not supported by a well established utility for the reasons set forth in the rejection under 35 USC 101 above, one skilled in the art clearly would not know how to use the claimed invention for practical benefits.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

The instant specification does not contain a written description of the invention in such full, clear, concise, and exact terms or in sufficient detail that one skilled in the art can reasonably conclude that applicant had possession of the claimed invention at the time of filing.

Claims 1-4, 7-10, 19, 50-53 are rejected under 35 USC 112, first paragraph.

Claims 1-4, 7-10, 19, 50-53 are drawn to:

1) An isolated nucleic acid comprising a nucleotide sequence encoding a "mammalian", "murine" or "human Ese1" (claims 1-4),

2) A "genomic" sequence of a mammalian Ese1 (claim 4).

3) A "complement" sequence of an isolated nucleic acid comprising a nucleotide sequence of at least 10 consecutive nucleotides, selected from the group consisting of SEQ ID NO:1, 2, , wherein said sequence is used as a probe or a primer (claims 7-8).

4) A recombinant vector comprising "said nucleic acid of claim 1, 7", and a host cell comprising said vector (claims 9-10, 50-51), and

5) A process for recombinantly producing "murine Ese1 protein", comprising culturing a host cell comprising a recombinant vector comprising "the nucleic acid of claim 2, or claim 3 or claim 4" (claims 19, 52-53).

The disclosure of the specification has been set forth above, under 101 rejection.

It is noted that although the specification discloses human Ese1, there is no disclosure of the actual structure of said human Ese1.

It is also noted that a nucleotide sequence encoding a "mammalian Ese1" encompasses any variant of Ese1, i.e variants from any mammalian species such as pig, monkey, cat etc....

It is further noted that a nucleotide encoding a "murine" or "human Ese1" encompasses wild type and any variant of murine wild type Ese1 of SEQ ID NO:1 or 2, and any variant of wild type human Ese1.

Moreover, it is noted that a complement could be a partial or complete complement, wherein a partial complete could share with SEQ ID NO:1 or 2 at least 10 complementary nucleotides. In other words, the claimed complement sequences encompass unrelated polynucleotide sequences that share with SEQ ID NO:1 or 2 at least 10 nucleotides.

Further, it is noted that there is no disclosure of the actual structural sequence for the claimed "genomic" sequence in claim 4.

Thus the claims encompass:

1) numerous structural variants of SEQ ID NO:1 or 2, with unknown structure, and

2) genomic DNA comprising the murine Ese1 of SEQ ID NO:1 or 2 or variants thereof, or comprising any mammalian Ese1 .

The findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. clearly are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "'naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here.

Thus, the instant specification may provide an adequate written description of the mammalian, murine or human Ese1, or complements of SEQ ID NO:1 or 2, or the genomic DNA, per Lilly by structurally describing a representative number of the mammalian, murine or human Ese1, or complements of SEQ ID NO:1 or 2, or the genomic DNA or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per

Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not describe the mammalian, murine or human Ese1, or complements of SEQ ID NO:1 or 2, or the genomic DNA in a manner that satisfies either the Lilly or Enzo standards. The specification does not provide the complete structure of any the mammalian, murine or human Ese1, or complements of SEQ ID NO:1 or 2, or the genomic DNA, other than the murine Ese1 of SEQ ID NOs: 1 and 2, and a splice variant of the murine Ese1 of SEQ ID NO:22 and its coding sequence of SEQ ID NO:23, , nor does the specification provide any physical or chemical characteristics of such nucleic acid molecules, other than the murine Ese1 of SEQ ID NOs: 1 and 2, and a splice variant of the murine Ese1 of SEQ ID NO:22 and its coding sequence of SEQ ID NO:23, nor any functional characteristics coupled with a known or disclosed correlation between structure and function. Although the specification discloses a single polynucleotide comprising SEQ ID NOs: 1, its coding region of SEQ ID NO: 2, and a single splice variant of the murine Ese1 of SEQ ID NO:22 and its coding sequence of SEQ ID NO:23, this does not provide a description of the mammalian, murine or human Ese1, or complements of SEQ ID NO:1 or 2, or the genomic DNA, that would satisfy the standard set out in Enzo.

The specification also fails to describe the mammalian, murine or human Ese1, or complements of SEQ ID NO:1 or 2, or the genomic DNA by the test set out in Lilly.

The specification describes only a single polynucleotide comprising SEQ ID NOs: 1, its coding region of SEQ ID NO: 2, and a single splice variant of the murine Ese1 of SEQ ID NO:22 and its coding sequence of SEQ ID NO:23. Therefore, it necessarily fails to describe a "representative number" of such species. In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

Thus, the specification does not provide an adequate written description of the mammalian, murine or human Ese1, or complements of SEQ ID NO:1 or 2, or the genomic DNA, that is required to practice the claimed invention.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

1. If Applicant could overcome the above 112, first paragraph above, claims 1-4, 7-10, 19, 50-53 are still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the murine Ese1 of SEQ ID NO:1 or 2, **does not reasonably provide enablement for a nucleic acid encoding "mammalian" or "human" or "murine Ese1", or "complements" of SEQ ID NO:1 or 2**. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-4, 7-10, 19, 50-53 are drawn to:

1) An isolated nucleic acid comprising a nucleotide sequence encoding a "mammalian", "murine" or "human Ese1" (claims 1-4).

2) A "complement" sequence of an isolated nucleic acid comprising a nucleotide sequence of at least 10 consecutive nucleotides, selected from the group consisting of SEQ ID NO:1, or 2, wherein said sequence is used as a probe or a primer (claims 7-8).

3) A recombinant vector comprising "said nucleic acid of claim 1, 7", and a host cell comprising said vector (claims 9-10, 50-51), and

4) A process for recombinantly producing "murine Ese1 protein", comprising culturing a host cell comprising a recombinant vector comprising "the nucleic acid of claim 2, or claim 3 or claim 4" (claims 19, 52-53).

It is noted that there is no disclosure of the actual structural sequence for the claimed nucleotide sequence encoding a human Ese1, which would be a variant of the murine Ese1.

In addition, it is noted that the specification discloses that novel mammalian proteins have been disclosed containing both EH and SH3 domains, named Ese1 and Ese2, wherein Ese is for EH domain and SH3 domain regulator of Endocytosis (p. 2, last paragraph bridging p.3). Thus based on the disclosure in the specification, one would reasonably interpret that Ese1 nucleic acid encompasses any nucleic acid provided it encodes a protein that has an EH domain and a SH3 domain, and which regulates endocytosis.

It is also noted that a nucleotide sequence encoding a "mammalian Ese1" encompasses any variant of Ese1, i.e variants from any mammalian species such as pig, monkey, cat etc....

It is further noted that a nucleotide encoding a "murine" or "human Ese1" encompasses wild type and any variant of murine wild type Ese1 of SEQ ID NO:1 or 2, and any variant of wild type human Ese1.

Moreover, it is noted that a complement could be a partial or complete complement, wherein a partial complete could share with SEQ ID NO:1 or 2 at least 10 complementary nucleotides. In other words, the claimed complement sequences encompass unrelated polynucleotide sequences that share with SEQ ID NO:1 or 2 at least 10 nucleotides.

The scope of the claims includes numerous structural variants with unknown structure. Applicants have not shown how to make and use the claimed variants which are capable of functioning or have the properties of the polynucleotide of SEQ ID NO:1 or 2, as that which is being disclosed.

The claimed variants have any type of substitution besides conservative substitution, at any nucleotide, throughout the length of the polynucleotide, as well as insertions and deletions. The specification and the claims do not place any limit on which nucleotide to be subjected to conservative or non-conservative substitution, the type of substitution besides conservative substitution, nor the type of nucleotides replacing the original nucleotides. Thus the scope of the claims includes structural variant nucleotide sequences encoding numerous structural variant polypeptide. Although the specification discloses that the types of changes are routinely done in the art, the specification and the claims do not provide any guidance as to which nucleotides to be substituted, or to which type of substitution besides conservative

substitution, or which nucleotide could be deleted or inserted so that the claimed polynucleotide could function as contemplated.

One cannot extrapolate the teaching in the specification to the scope of the claims because one cannot predict that the claimed variants would have biological activity or properties related to that of SEQ ID NO:1 or 2. The following teaching of the art, although drawn to proteins, would apply as well the claimed polynucleotide variants of SEQ ID NO:1 or 2, because polynucleotide sequences encode proteins. It is well known in the art that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, Bowie et al (Science, 1990, 257 : 1306-1310) teach that an amino acid sequence encodes a message that determine the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instruction of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (col.1, p.1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitution can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative

substitutions or no substitutions (col.2, p.1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al, (Journal of Cell Biology, 1990, 11: 2129-2138), who teach that replacement of a single lysine residue at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (Lazar et al. Molecular and Cell Biology, 1988, 8: 1247-1252). Similarly, it has been shown that aglycosylation of antibodies reduces the resistance of the antibodies to proteolytic degradation, while CH2 deletions increase the binding affinity of the antibodies (see Tao. et al. The Journal of Immunology, 1989, 143(8): 2595-2601, and Gillies et al. Human Antibodies and Hybridomas, 1990, 1(1): 47-54). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein.

The specification does not disclose how to make the claimed nucleic acid molecules, such that they would function or have the properties as claimed, or how to use said nucleic acid molecules if they did not have the function or properties claimed.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

2. If Applicant could overcome the above 112, first paragraph above, claims 4, 53 are still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SEQ ID NO:1 or 2, **does not reasonably provide enablement for a "genomic DNA" comprising a mammalian Ese1**. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 4, 53 are drawn to:

a) An isolated nucleic acid comprising a nucleotide sequence encoding a mammalian Ese1, which is a genomic sequence (claim 4), and

b) A process for recombinantly producing murine Ese1 protein, comprising culturing a host cell comprising a vector comprising the nucleic acid of claim 4 (claim 53).

The specification discloses the mouse cDNA sequence of SEQ ID NO:1 (p.38-42) and its coding sequence of SEQ ID NO:2 (p.38-42).

There is no disclosure of the genomic DNA sequence comprising the murine Ese1 of SEQ ID NO:1 or 2 or human Ese1.

On cannot extrapolate the teaching in the specification to the scope of the claim. The specification fails to identify and describe the 5' and 3' regulatory regions and untranslated regions essential to the function of the claimed invention, which are required since the claimed invention currently encompasses the gene. The art indicates that the structures of genes with naturally occurring regulatory elements and untranslated regions is empirically determined (Harris et al. J. of The Am Society of

Nephrology 6:1125-33, 1995; Ahn et al. Nature Genetics 3(4):283-91, 1993; and Cawthon et al. Genomics 9(3):446-60, 1991). Therefore, the structure of these elements is not conventional in the art and it would be undue experimentation for one of skill in the art to practice the claimed invention.

3. If Applicant could overcome the above 112, first paragraph above, claims 10, 19, 51-53 are still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated host cell comprising a vector comprising SEQ ID NO:1 or 2, **does not reasonably provide enablement for "a host cell"** comprising a vector comprising a mammalian, murine, or human Ese1 or SEQ ID NO:1 or 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 10, 19, 51-53 are drawn to a host cell comprising a recombinant vector comprising the mammalian Ese1 or SEQ ID NO:1 or 2, or complement thereof (claims 10, 51), and

4) A process for recombinantly producing murine Ese1 protein, comprising culturing a host cell comprising a vector comprising the nucleotide sequence encoding murine Ese1, or human Ese1 (claims 19, 52-53).

The specification contemplates gene therapy, using retroviral vectors comprising Ese gene (p.26, last paragraph to p.28).

There is however no teaching in the specification of how to successfully produce in vivo host cells that express the claimed Ese gene, nor actual data of producing in vivo host cells that express the claimed Ese gene.

The claims 10, 19, 51-53 encompass an in vivo host cell from gene therapy, and a method of recombinantly producing murine Ese1 protein, comprising culturing said host cell.

On cannot extrapolate the teaching in the specification to the scope of the claim. The state of the art at the time of filing was that the combination of vector, promoter, protein, cell, target tissue, level of expression and route of administration required to target the tissue of interest and obtain a therapeutic effect using gene therapy was unpredictable. For example, Miller (1995, FASEB J., Vol. 9, pages 190-199) review the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma (Sept. 1997,

Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Crystal (1995, Science, Vol. 270, page 404-410) also reviews various vectors known in the art and indicates that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409).

It is noted that MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature ot the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In constrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling."

In view of the unpredictability of gene therapy, and the lack of disclosure of how to successfully produce in vivo host cells that express the claimed Ese gene, it would be undue experimentation for one of skill in the art to practice the claimed invention.

4. If Applicant could overcome the above 112, first paragraph above, claim 52 is still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process for recombinantly producing murine Ese1 protein, comprising culturing an isolated host cell comprising a vector comprising SEQ ID NO:1 or 2, **does not reasonably provide enablement for a process for recombinantly producing "murine" Ese1 protein, comprising culturing an isolated host cell comprising a vector comprising a nucleotide sequence encoding a "human" Ese1 protein.** The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 52 is drawn to a process for recombinantly producing murine Ese1 protein, comprising culturing an isolated host cell comprising a vector comprising a nucleotide sequence encoding a human Ese1 protein.

The Examiner takes note that although the specification does not disclose the structure of the nucleic acid molecule encoding a human Ese1 protein, one would expect that said human nucleic acid encoding human Ese1 protein is a variant of and different in structure from the nucleic acid molecule encoding murine Ese1 protein, because it is well known in the art that variation in sequence structure among different mammalian species is common phenomena.

One would not have expected that the human nucleotide sequence encoding human Ese1 protein would be translated into a murine Ese1 protein, because the human nucleotide sequence encoding human Ese1 protein is expected to be structurally different from the murine nucleotide sequence encoding murine Ese1 protein.

The specification does not disclose how to produce murine Ese1 protein, using the human nucleotide sequence encoding human Ese1 protein.

In the absence of a teaching of how to produce murine Ese1 protein, using the human nucleotide sequence encoding human Ese1 protein, the unpredictability of producing a murine Ese1 by culturing a host cell comprising a vector comprising a human Ese1 sequence, it would be undue experimentation for one of skill in the art to practice the claimed invention.

REJECTION UNDER 35 USC 102(b or e)

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the

applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

1. Claims 7-8 are rejected under 35 USC 102(b) as anticipated by Sparks, AB et al, Genbank Sequence Database (Accession U61166), National Center for Biotechnology Information, National Library of Medicine, Bethesda, Maryland, or Nat. Biotechnol, 14(6): 741-744, 1996.

Claim 7 is drawn to an isolated nucleic acid comprising a nucleotide sequence of at least 10 consecutive nucleotides, selected from the group consisting of a "complement" of any of the sequence of SEQ ID NO:1 or 2.

Claim 8 is drawn to the nucleic acid of claim 7, wherein said sequence is used as a probe or a primer.

It is noted that a complement could be a partial or complete complement, wherein a partial complete could share with SEQ ID NO:1 or 2 at least 10 complementary nucleotides. In other words, the claimed complement sequences encompass unrelated polynucleotide sequences that share with SEQ ID NO:1 or 2 at least 10 nucleotides.

It is further noted that the limitation in claim 8, that the sequence of claim 7 used as a probe or a primer, is viewed as a recitation of intended use and therefore is not given patentable weight in comparing the claims with the prior art. Claim 8 reads on the ingredient *per se*, which is an isolated nucleic acid comprising a nucleotide sequence of at least 10 consecutive nucleotides, selected from the group consisting of a "complement" of any of the sequence of SEQ ID NO:1 or 2.

Sparks AB et al teach a sequence, which is 69% similar to SEQ ID NO:1 from nucleotide 2112 to nucleotide 5061, under MPSRCH sequence similarity search (MPSRCH search report, 2003, us-09-674-273a-1.rge, pages 28-30).

Given the polynucleotide sequence taught by Sparks et al, one of ordinary skill in the art would immediately envision the claimed complementary sequence.

2. Claims 7-8, 50-51 are rejected under 35 USC 102(e) as anticipated by US20020034755A1, which is a divisional of SN=08/630915, filed on 04/03/1996, now patented as US=6,309,820 B1.

Claim 7 is drawn to an isolated nucleic acid comprising a nucleotide sequence of at least 10 consecutive nucleotides, selected from the group consisting of a "complement" of any of the sequence of SEQ ID NO:1 or 2.

Claim 8 is drawn to the nucleic acid of claim 7, wherein said sequence is used as a probe or a primer.

Claims 50-51 are drawn to a recombinant vector comprising an isolated nucleic acid comprising a nucleotide sequence of at least 10 consecutive nucleotides, selected from the group consisting of a complement of any of the sequence of SEQ ID NO:1, or 2, and a host cell comprising said vector (claims 50-51).

It is noted that a complement could be a partial or complete complement, wherein a partial complete could share with SEQ ID NO:1 or 2 at least 10 complementary nucleotides. In other words, the claimed complement sequences encompass unrelated polynucleotide sequences that share with SEQ ID NO:1 or 2 at least 10 nucleotides.

It is further noted that the limitation in claim 8, that the sequence of claim 7 used as a probe or a primer, is viewed as a recitation of intended use and therefore is not given patentable weight in comparing the claims with the prior art. Claim 8 reads on the ingredient *per se*, which is an isolated nucleic acid comprising a nucleotide sequence of

at least 10 consecutive nucleotides, selected from the group consisting of a "complement" of any of the sequence of SEQ ID NO:1 or 2.

US20020034755A1 or US 6,309,820 teach a sequence, SEQ ID NO:193, which is 60% similar to SEQ ID NO:2 from nucleotide 2609 to nucleotide 3642, under MPSRCH sequence similarity search (MPSRCH search report, 2003, us-09-674-273a-2.rnpb, pages 6-7).

US 6,309,820 further teaches insertion of the isolated gene into a cloning vector and transformation of a host cell with said vector (column 35, last paragraph, bridging column 36) for generation a large quantities of the recombinant DNA molecule.

Given the polynucleotide sequence taught by US20020034755A1 or US=6,309,820, one of ordinary skill in the art would immediately envision the claimed complementary sequence, vector and host cell.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 703-305-2008. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ANTHONY CAPUTA can be reached on 703-308-3995. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.

MINH TAM DAVIS

PATENT EXAMINER

December 19, 2003

12/30/03

EXAMINER'S REMARK

1. I did not do the 103, because it is not clear that the sequence in the art has any utility.

2. No new matter for claim 52, which has support in original claim 19.

3. Eps15 could not be used for 102, because it does not have SH3 domain, although it has SH3-binding motif.

4. Intersectin and Dap160 have both EH domain and SH3 domain (specification, page 10, last paragraph).

However, human intersectin is published only in Nov 1998, after the priority date.

No human or mammalian version of Drosophila Dap160 is found.

CONSULTATION WITH SPE ANTHONY CAPUTA

1) Claims drawn to mammalian, murine and human Ese1 without being accompanied by a SEQ ID NO, are rejected under written description and scope.

CONSULTATION WITH SPE ANTHONY CAPUTA, and YVONNE EYLER

Claim 8 is included with claim 7 under 102 rejection, as intended use.

CONSULTATION WITH SPECIALIST BRIAN STANTON (01/06/03)

1) Although the claimed nucleic acid could block endocytosis, the claimed nucleic acids are still rejected under 101 utility. Applicant needs to assert what blocking endocytosis could actually be used for practical purpose.

2) Recitation of Ese1 alone, without SEQ ID NO: reads on variants of Ese1.